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Left Prefrontal Repetitive Transcranial Magnetic Stimulation in Schizophrenia

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Abstract

In a double-blind, controlled study, we examined the therapeutic effects of high-frequency left prefrontal repetitive transcranial magnetic stimulation (rTMS) on schizophrenia symptoms. A total of 22 chronic hospitalized schizophrenia patients were randomly assigned to 2 weeks (10 sessions) of real or sham rTMS. rTMS was given with the following parameters: 20 trains of 5-second 10-Hz stimulation at 100 percent motor threshold, 30 seconds apart. Effects on positive and negative symptoms, self-reported symptoms, rough neuropsychological functioning, and hormones were assessed. Although there was a significant improvement in both groups in most of the symptom measures, no real differences were found between the groups. A decrease of more than 20 percent in the total PANSS score was found in 7 control subjects but only 1 subject from the real rTMS group. There was no change in hormone levels or neuropsychological functioning, measured by the MMSE, in either group. Left prefrontal rTMS (with the used parameters) seems to produce a significant nonspecific effect of the treatment procedure but no therapeutic effect in the most chronic and severely ill schizophrenia patients.

Keywords: rTMS, schizophrenia, prefrontal hypometabolism, RCT.

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Repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex (DLPFC) has been studied mainly as a therapeutic tool for major depression (Pascual-Leone et al. 1996; George et al. 1997). High-frequency rTMS has been reported to normalize the hypoactive left DLPFC found in some depressed patients (George et al. 1995).

There have been reports that patients with schizophrenia have decreased metabolic activity in the prefrontal cortex (Andreasen et al. 1997). In a volumetric study on schizophrenia patients, negative symptoms correlated with white matter reductions in the prefrontal region (Sanfilipo et al. 2000). Functional imaging studies have suggested that hypoactivity of the left DLPFC correlates with psychomotor poverty or retardation (Wolkin et al. 1992). Moreover, a preliminary study suggests that DLPFC function actually mediates negative symptoms (Nahas et al. 2000).

Some preliminary rTMS studies have demonstrated improvement in mood (Geller et al. 1997) and in anxiety and restlessness (Feinsod et al. 1998) as well as in negative symptoms (Cohen et al. 1999) in schizophrenia patients. A single case of beneficial effects of rTMS in catatonia has been published (Grisaru et al. 1998).

Three treatment studies of rTMS in schizophrenia patients have been published thus far; low-frequency left temporoparietal rTMS seems to reduce auditory hallucinations in schizophrenia patients (Hoffman et al. 2000), low-frequency right prefrontal rTMS over 2 weeks had no effect on symptoms of schizophrenia (Klein et al. 1999), and high-frequency left prefrontal rTMS showed some therapeutic effect on symptoms in a recent preliminary study (Rollnik et al. 2000). We examined the effect of left DLPFC rTMS for 2 weeks in schizophrenia patients in a parallel group, randomized double-blind controlled trial.

Method

We recruited 22 chronic inpatients from Vanha Vaasa Hospital, a state mental hospital in western Finland, with a Structured Clinical Interview for *DSM–IV*–verified (SCID; First et al. 1995) *DSM–IV* diagnosis of schizophrenia (APA 1994). Of these patients, 19 were men and 20 were right-handed. Those with major physical or neurological abnormalities were excluded. After a complete description of the study was presented, written informed consent was obtained and patients were randomly

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assigned to real or sham treatment. Concealment of the allocation was guaranteed by opening the closed randomization envelopes just before the first stimulation of the first session. Of the 22 patients, 10 had paranoid, 1 catatonic, 3 hebephrenic, 6 undifferentiated, and 2 residual schizophrenia.

At baseline, the groups receiving active rTMS and sham stimulation did not differ significantly in gender, inpatient status, or history of alcohol abuse. Their mean ages were 38.5 (standard deviation [SD] = 10.2) and 34.8 (SD = 9.8), respectively. The mean duration of the current hospitalization was 4.2 (SD = 4.6) and 4.5 (SD = 4.0) years, and the total duration of the illness was 13.5 (SD = 8.9) and 12.9 (SD = 12.0) years, respectively. The mean Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987) total value, indicating the severity of the illness, was 105.2 (SD = 41.2) and 110.3 (SD = 20.2), respectively. There were no statistically significant differences in any of the baseline values.

We allowed an unlimited but stable concomitant drug therapy. Among the 11 patients receiving rTMS, concomitant drug therapy mainly consisted of clozapine for 7 patients (1 combined with risperidone, and 1 with olanzapine), olanzapine for 2, quetiapine for 1, and zuclopenthixol for 1 patient. The mean chlorpromazine equivalent dose was 1,168 mg. In the rTMS group, 4 also received a selective serotonin reuptake inhibitor (SSRI), 3 were on a mood stabilizer (valproate or oxcarbazepine at a therapeutic level), and 5 received benzodiazepines (mean lorazepam equivalent dose 4.6 mg).

Among the 11 patients receiving sham treatment, concomitant drug therapy consisted mainly of clozapine for 7 patients and olanzapine for 4 patients. The mean chlorpromazine equivalent dose was 1,309 mg. In the sham group, 4 also received an SSRI, 3 were on a mood stabilizer (valproate or oxcarbazine at a therapeutic level), and 3 received benzodiazepines (mean lorazepam equivalent dose 4 mg). There were no statistically significant differences in concomitant antipsychotic or other drug treatments between the two groups. The doses of the drugs were stable throughout the trial.

Transcranial magnetic stimulation was administered by a 70-mm figure eight–shaped coil (Magstim Co., U.K.) to the left DLPFC (measured as 5 cm anterior to the optimal site for activating the right abductor pollicis brevis) with the following safety guideline–fulfilling characteristics: 10 Hz, 100 percent motor threshold, 20 trains of 5 seconds each, 30 seconds apart. The stimulation parameters were taken from earlier depression studies and have been suggested to have DLPFC-activating properties (e.g., Pasqual-Leone et al. 1996). The threshold was determined at rest with surface electromyography, by using the method of limits (i.e., the intensity required to evoke at least a 50-μV peak-to-peak potential in four out of eight trials over the optimal site). The coil was tangential to the scalp at 45° to the parasagittal line, with the handle pointing backward in the real rTMS condition. In the sham condition, the coil was held at 90° to the scalp with both wings touching the scalp.

Psychiatrists (M.E., K.T., P.T.) blind to the treatment groups assessed symptoms at baseline and at the end of 2 weeks' rTMS. The Mini Mental State Examination (MMSE; Folstein et al. 1975), for rough cognitive functioning, and the PANSS were assessed at both time points. Serum cortisol, thyroid-stimulating hormone (TSH), and prolactin concentrations as well as the motor threshold were measured at these time points. A self-report questionnaire, Symptom Checklist–90 (SCL–90; Derogatis et al. 1973), was filled out by the patients at pre- and posttesting. Self-reports are rarely used with psychotic patients, but we used the SCL–90 along with the PANSS to get patients' subjective views on the possible symptom change.

The rating scale scores and the laboratory values for all patients were analyzed for change over the 2-week treatment period. A paired sample 2-tailed t test was used to examine the significance of change within the groups. The size of any change in the rTMS and sham groups was compared by an independent sample 2-tailed t test. Intention-to-treat analysis was used, and a 20 percent decrease in the patient's total PANSS score was defined as our primary outcome measure.

Results

Seven patients of the sham group but only one of the rTMS group were improved according to our primary outcome measure—a 20 percent decrease in the total PANSS score. The chi-square test indicated a statistically significant difference between the groups (Fisher's 2-sided exact test, $p = 0.024$).

There were no significant differences between the two groups in the different PANSS scales. A significant improvement over the 2 weeks in all the PANSS scales was found within the sham group, whereas within the rTMS group significant improvement was found in only the positive symptom scale and the total PANSS score (table 1).

There were no significant differences between the two groups in the self-report measures (table 1).

No significant changes were found in the hormone levels, aside from a small decrease in the TSH value within the sham group. No differences between the groups were found in the hormone levels.

There was a slight increase in the motor threshold in the rTMS group (table 1). No significant difference

Table 1. Effect of 2 weeks of real or sham left DLPFC high-frequency rTMS in schizophrenia, and the statistical significance of change within and between groups

	rTMS ($n = 11$)					Sham ($n = 11$)					Comparison		
			Change Within Group[1]					Change Within Group[1]			Change Between Groups[2]		
Measure	**Mean**	**(SD)**	***t***	***df***	***p***	**Mean**	**(SD)**	***t***	***df***	***p***	***t***	***df***	***p***
PANSS positive													
Pre-	23.6	(10.7)				27.0	(5.6)						
Post-	20.0	(9.1)				19.1	(7.4)						
Change	–3.6	(4.7)	2.40	9 0.	040	–7.9	(7.1)	3.68	10	0.004	–1.61	19	0.123
PANSS negative													
Pre-	28.9	(11.5)				31.0	(7.7						
Post-	27.5	(10.9)				25.2	(5.8)						
Change	–1.4	(3.4)	1.30	9 0.	226	–5.8	(7.1)	2.71	10	0.022	–1.79	19	0.090
PANSS general													
Pre-	52.1	(23.4)				52.3	(10.9)						
Post-	48.0	(17.8)				44.6	(12.6)						
Change	–4.1	(7.7)	1.68	9	0.127	–7.7	(8.9)	2.8	10	0.018	–0.97	19	0.346
PANSS total													
Pre-	105.2	(41.2)				110.3	(20.2)						
Post-	92.3	(34.3)				85.6	(23.9)						
Change	–12.3	(13.9)	2.86	9	0.019	–24.7	(20.2)	4.04	10	0.002	–1.62	19	0.121
SCL–90: GSI													
Pre-	0.99	(0.57)				1.06	(1.04)						
Post-	0.73	(0.56)				0.78	(0.86)						
Change	–0.26	(0.34)	2.43	9 0.	038	–0.28	(0.53)	1.76	10	0.110	–0.08	19	0.936
SCL–90: DEP													
Pre-	1.34	(0.77)				1.37	(1.24)						
Post-	0.83	(0.69)				0.82	(0.79)						
Change	–0.46	(0.54)	2.87	9	0.019	–0.55	(0.52)	2.16	10	0.056	0.56	19	0.580
SCL–90: PSY													
Pre-	0.83	(0.75)				0.93	(1.14)						
Post-	0.50	(0.60)				0.51	(0.53)						
Change	–0.33	(0.47)	1.80	9	0.090	–0.42	(0.81)	0.89	10	0.397	0.18	19	0.860

Table 1. Effect of 2 weeks of real or sham left DLPFC high-frequency rTMS in schizophrenia, and the statistical significance of change within and between group—Continued

	rTMS ($n = 11$)						Sham ($n = 11$)				Comparison			
			Change Within Group[1]				Change Within Group[1]				Change Between Groups[2]			
Measure	Mean	(SD)	*t*	*df*	*p*	Mean	(SD)	*t*	*df*	*p*	*t*	*df*	*p*	
Motor threshold														
Pre-	55.9	(9.8)				63.2	(8.8)							
Post-	58.9	(12.1)				63.9	(9.9)							
Change	3.0	(3.3)	−2.88	9	0.018	0.7	(3.7)	−0.60	9	0.566	−1.46	18	0.160	

Note.—DEP = Depression subscale; DLPFC = dorsolateral prefrontal cortex; GSI = General Severity Index; PANSS = Positive and Negative Syndrome Scale; pre- = pretreatment value; post- = posttreatment value; PSY = Psychoticism subscale; rTMS = repetitive transcranial magnetic stimulation; SCL–90 = Symptom Checklist–90; SD = standard deviation.

[1] Paired-sample 2-tailed *t* test.

[2] Independent-sample 2-tailed *t* test.

between the two groups was found. There was no change in the MMSE scores within either group.

In the rTMS group no significant differences were found in any of the outcome measures between those who were on anticonvulsant drugs and those who were not. No differences were found in the outcome measures between those using benzodiazepines and those not using them, apart from the PANSS general symptoms scale, where those using benzodiazepines improved significantly more (2-tailed independent samples *t* test, $p = 0.036$) than did the nonusers.

One patient in each group dropped out because of paranoid thoughts about the treatment. The sham group dropout had received 5 days of treatment and could be rated at the end of the 2-week period, whereas the rTMS dropout stopped the trial during the first session and refused further ratings. No seizures or other side effects, besides a mild headache in three patients of the rTMS group, occurred during the trial. Most of the patients in the rTMS group (8 out of 11) but none in the sham group considered the stimulation painful.

Discussion

The results suggest that high-frequency rTMS of the left DLPFC with the parameters used in this study does not have significant therapeutic effects in severe schizophrenia. Our results do not support the preliminary finding that high-frequency rTMS to the left DLPFC improves symptoms of schizophrenia (Nahas et al. 2000; Rollnik et al. 2000).

This study detected an impressive nonspecific effect for the entire rTMS procedure but no specific effect for the magnetic brain stimulation. In earlier rTMS studies, the possibility of active sham forms has been discussed (Loo et al. 2000). In this study, the coil was held at 90° off the scalp, which does not give a rTMS-like scalp sensation, but also causes no stimulation to the cortex, thus ruling out the possibility of an active sham (Loo et al. 2000). Rollnik's high-frequency rTMS study used a crossover design, and the stimulation coil was at 45° off the scalp under the sham condition (Rollnik et al. 2000), thus making a carryover effect possible.

Our study sample was small, which creates the possibility of a type II error. However, the control group seemed to improve more than the rTMS group, although not statistically, which reduces the possibility that we did not detect an existing rTMS effect. Interestingly, self-reported symptom severity was the only measure where only the rTMS group improved significantly (0.5 SD improvement). Still, as in the other measures, there was no statistical difference between the groups. The finding of no difference in the change of motor threshold between

the groups is similar to a recently published finding (Dolberg et al. 2002).

The patients in our study were chronic, severely ill (PANSS > 100), heavily medicated schizophrenia patients, which may partly explain the lack of effect for this short treatment period. The patients in Rollnik et al.'s study (2000) were less severely ill and were not reported to be using anticonvulsant drugs. In Hoffman et al.'s study (2000), anticonvulsant drugs reduced the rTMS effects, which is not probable in this study, because there was no difference in the outcome of users and nonusers of these drugs. Also, the use of benzodiazepines could theoretically reduce the rTMS effect, as they have been reported to reduce cortical excitability (Ziemann et al. 1996). In this study, the only difference between users and nonusers of benzodiazepines was found in the PANSS general symptoms scale, and surprisingly, it favored the users.

Rollnik et al. used fast rTMS of slightly different characteristics (e.g., they employed 20 Hz frequency, while this study used 10 Hz frequency), which may partly explain the different result.

Finally, the malfunctioning at the prefrontal cortex in patients with chronic schizophrenia may involve mechanisms different from those involved in depression. The malfunctioning may be, even if qualitatively similar, more permanent than in depressive patients, consequently requiring longer treatment periods (e.g., Dolberg et al. 2002) or stronger stimulation (possibly even outside published safety guidelines) to produce a response.

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